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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,681	BEHL ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-56* is/are pending in the application.

4a) Of the above claim(s) *22-25,35-37 and 41-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-34 and 40* is/are rejected.

7)☒ Claim(s) *38 and 39* is/are objected to.

8)☒ Claim(s) *22-56* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with** traverse of Group II (claims 26-34 and 38-40) in the Response to Restriction Requirement filed 23 September 2003 is acknowledged. The traversal is on the ground(s): (a) Group II is not solely limited in scope to proteins comprising SEQ ID NO: 2, SEQ ID NO: 4, and composition comprising same, (b) search and examination of the entire application could be made without serious burden, (c) prosecution of five separate patent applications would place undue financial hardship on Applicants.

2. These reasons are not found persuasive because although the claims within Group II may encompass embodiments beyond SEQ ID NO: 2 and SEQ ID NO: 4 and compositions thereof, the Examiner grouped them together because of their relation in view of sharing a special technical feature, namely a protein which is a human semaphorin 6a-1 [MPEP §1893.03(d)]. It is noted that Group II includes SEQ ID NO: 1, 2, 3, and 4, all four will be considered. Applicant's traversal of the description of the claims in the Restriction Requirement mailed 28 August 2003 does not in and of itself constitute a rebuttal of the search and examination burden set forth in the last Office Action (Restriction Requirement, 28 August 2003). Secondly, for the reasons set forth in the last Office Action (Restriction Requirement, 28 August 2003) the claims as presented represent five distinct and independent inventions thus represents an undue search and examination burden on the Examiner. Finally, concerning prosecution costs are not under control of the Examiner and are not considered for purposes of examination (35 U.S.C. §3). However, in the interest of compact prosecution of patent applications, Examiners take all non-elected material into consideration for purposes of rejoinder upon reaching allowable subject matter.

Claims **22-25, 35-37,** and **41-56** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

3. The Examiner notes that according to USPTO records, only claims 22-56 are currently pending in the instant application. Applicant cancelled claims 1-21 and added claim 22 in a Preliminary Amendment filed 22 May 2001. Then in a Supplemental Preliminary Amendment filed 25 January 2001, Applicant added claims 22-56. The Restriction Requirement (28 August 2003) was performed on the claims as amended. Therefore only claims 22-56 are currently pending.

4. Claims **26-34** and **38-40** are currently under examination.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: A-G in Figure 4, A-C in Figure 5, and A-B in Figure 7. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. This application discloses an amino acid sequence in Figures 1, 2, and 6 without the accompanying SEQ ID NO's. Correction is required.

Claim Objections

7. Claim **34** is objected to because of the following informalities: claim 34 depends from claim 22, a non-elected claim and is therefore not drawn to the invention under examination. Appropriate correction is required.

8. Claims **38** and **39** are objected to because of the following informalities: both claims depend from rejected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims **26-34** are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to "a protein" which is a product of nature and therefore non-statutory subject matter. Applicant may obviate this rejection by amending the claims to read "An isolated" or "A substantially purified" protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **27, 28, 30, 31, 34,** and **40** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated protein comprising SEQ ID NO: 2, SEQ ID NO: 4, and/or encoded by SEQ ID NO: 1, SEQ ID NO: 3 and compositions thereof*, does not reasonably provide enablement for *proteins further comprising a substitution thereto, a deletion thereto, or an addition thereto of single amino acids or short amino acid sections, or compositions thereof.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** the invention commensurate in scope with these claims.

11. The claims are drawn very broadly to mutants, variants, and derivatives of SEQ ID NO: 2 and SEQ ID NO: 4 as well as proteins encoded by either SEQ ID NO: 1 or SEQ ID NO: 3. The language of said claims encompasses mutations such as substitutions, frame-shift mutations, truncations, point mutations, duplications, insertions, and translation mistakes.

12. The specification teaches that SEQ ID NO: 1 encodes a human semaphorin 6A-1 protein ((HSA) SEMA6A-1: SEQ ID NO: 2) containing a Zyxin-like domain that binds to the

Ena/VASP-like protein (Evl). SEQ ID NO: 3 encodes a binding domain of human semaphorin 6A-1 protein (SEQ ID NO: 4).

13. The specification as filed fails to provide any guidance for the successful expression and characterization of substitutions, deletions, and/or additions in SEQ ID NO: 1-4, and since resolution of the various complications in regards to targeting the effects of any given mutation in a particular gene or protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of construction, expression, and characterization of a large group of mutant forms of SEQ ID NO: 2 and 4 and correlation with non-mutated isoforms. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention as it represents an invitation to experiment (MPEP §2164.01).

14. Additionally, a person skilled in the art would recognize that predicting the efficacy of using the prophetic guidance in the instant Specification to determine the viability of mutants of SEQ ID NO: 1-4 as highly problematic (see MPEP §2164.03). Thus, although the specification prophetically considers and discloses general methodologies of making the mutants, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;

(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

15. The following references are cited herein to illustrate the state of the art of protein biochemistry.

16. On the nature of the invention, Zhou *et al.* (January 1997) "Cloning and expression of a novel murine semaphorin with structural similarity to insect semaphorin I." Mol Cell Neurosci. **9**(1): 26-41 (**IDS #BD**) and Hall *et al.* (October 1996) "Human CD100, a novel leukocyte semaphorin that promotes B-cell aggregation and differentiation." PNAS **93**: 11780-11785 (**IDS #BF**) both teach that the semaphorin family is divided into five very diverse subfamilies each with different expression patterns (pp. 36). While sharing two distinct structure features: a signal sequence at the N-terminus and a characteristic extracellular "semaphorin" domain, the families are diverse, for instance some semaphorin family members are secreted and others are membrane bound (pp. 26). Thus the prior art teaches to the unpredictability of the effect of mutations on semaphorin family members as changing amino acids may completely alter the expression pattern, function, and location (secreted versus membrane bound) of the altered semaphorin family member.

17. On support in the prior art, Prehoda *et al.* (14 May 1999) "Structure of the Enabled/VASP Homology 1 Domain-Peptide Complex: A Key Component in the Spatial Control of Actin Assembly." Cell **97**: 471-480 (**IDS #AE**) teaches that the EVH1 domain recognize the general features of a proline-rich sequence but not all proline rich sequences (pp.

475-476). Therefore, a undue burden of experimentation is present for the skilled artisan to mutate SEQ ID NO: 1-4 to insure that the resultant mutant still binds a member of the Ena/VASP family of proteins as required in the claims.

18. Regarding the derivatives and fragments of the claimed proteins encompassed in the claims, the Examiner interprets this as encompassing variants of SEQ ID NO: 2 and SEQ ID NO: 4 as well as the numerous open reading frames of SEQ ID NO: 1 and 3. Thus the skilled artisan is confronted with the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein which is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the

nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art

which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of protein biochemistry to make and use mutations of SEQ ID NO: 1, 2, 3, and 4 as exemplified in the references herein.

20. Claims **27, 28, 30,** and **31** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to polypeptides having substitution, deletion, and/or addition mutations with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by any given variation from a disclosed sequence.

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the

claim that is sufficiently disclosed is a partial structure in the form of a recitation of mutated variants, derivatives, and fragments of the protein encoded by SEQ ID NO: 1 and 3. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described [MPEP §2163 II 3(a)]. The only adequately described species is a polypeptide encoded by SEQ ID NO: 1 and 3 (in the instant case, SEQ ID NO: 2 and 4 respectively). No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only isolated polypeptides comprising the amino acid sequence encoded by SEQ ID NO: 1 and 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

26. Claims **27, 28, 30,** and **31** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The term "short" in claims 27, 28, 30, and 31 is a relative term which renders the claim indefinite. The term "short" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the prior art and the specification as filed as to what constitutes a "short amino acid section". Thus the metes and bounds of the term are ambiguous.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claims **26, 27, 29, 30, 34,** and **40** are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/27205 (25 June 1998) Jacobs *et al.* (**IDS #AC**) WO 98/27205 teaches a protein encoded by a nucleic acid which shares 88.8% sequence homology with SEQ ID NO: 1 and proteins encoded therein thus meeting the limitations of claims 26 and 27 (pp. 69-71). WO 98/27205 teaches a protein encoded by a nucleic acid which shares 100% sequence homology with SEQ ID NO: 3 for a fragment comprising bp 1-216 and proteins encoded therein thus meeting the limitations of claims 29 and 30 (pp. 69-71). Further WO 98/27205 teaches a protein encoded by a nucleic acid which shares 100% sequence homology with SEQ ID NO: 3 for a fragment comprising bp 1-216 and is therefore identical to SEQ ID NO: 1 and the protein encoded by the fragment meets the limitations of claims 26, 27, 34, and 40 (sequence listing).

Summary

29. Claims **26-34** and **40** are hereby rejected.

30. Claims **26, 29, 32, 33, 38,** and **39** are free of the art.

31. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 2002/0055627 A1 (9 May 2002) Rosen *et al.*

b. US 2003/0003532 A1 (2 January 2003) Shimkets (discloses a sequence that shares 98.2% homology with SEQ ID NO: 1; 100% homology with SEQ ID NO: 3 for bp 1-216)

c. US 2003/0054514 A1 (20 March 2003) Shimkets & LaRochelle (discloses a sequence that shares 98.2% homology with SEQ ID NO: 1, 99.5% homology with SEQ ID NO: 2; 100% homology with SEQ ID NO: 3 for bp 1-216)

d. WO 00/53742 (14 September 2000) Shimkets (discloses a sequence that shares 98.2% homology with SEQ ID NO: 1)

e. Klostermann *et al.* (15 December 2000) "The Orthologous Human and Murine Semaphorin 6A-1 Proteins (SEMA6A-1/Sema6A-1) Bind to the Enabled/Vasodilator-stimulated Phosphoprotein-like Protein (EVL) via a Novel Carboxyl-terminal Zyxin-like Domain." The Journal of Biological Chemistry **275**(50): 39647-39653

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
October 30, 2003